

For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory Only.

GLUCRETA GM

1. Generic Name

Dapagliflozin, Glimepiride, Metformin Hydrochloride (Extended release) Tablets

2. Qualitative and quantitative Composition:

GLUCRETA GM 1

Each film coated bilayer tablet contains:

Dapagliflozin Propanediol USP

eq. to Dapagliflozin.....10 mg

Glimepiride I.P.1mg

Metformin Hydrochloride I.P.

(Extended Release).....1000 mg

Excipientsq.s.

Colour: Sunset Yellow Lake

The Excipients used are Xanthan gum, Acrypol, Talc, Polyvinylpyrrolidone K, Hydroxy propyl methyl cellulose, Acrypol, Colloidal Silicon dioxide, Magnesium Stearate, Micro Crystalline Cellulose, Lactose monohydrate, Isopropyl alcohol, Dichloromethane, Low Substituted hydroxyl propylcellulose, Crospovidone, Sunset Yellow Lake, Colloidal Silicon dioxide, Directly compressible Lactose, Magnesium Stearate, Dichloromethane.

GLUCRETA GM 2

Each film coated bilayer tablet contains:

Dapagliflozin Propanediol USP

eq. to Dapagliflozin.....10 mg

Glimepiride I.P.2 mg

Metformin Hydrochloride I.P.

(Extended Release).....1000 mg

Excipientsq.s.

Colour: Quinoline Yellow Lake

The Excipients used are Xanthan gum, Acrypol, Talc, Polyvinyl pyrrolidone k, Hydroxy propyl methyl cellulose, Acrypol, Colloidal silicon dioxide, Magneium Stearate, Micro crystalline Cellulose, Lactose Monohydrate, Isopropyl alcohol, dichloromethane, Low substituted hydroxyl propylcellulose, Crospovidone, Quinoline Yellow Lake, Directly compressible lactose

3. Dosage form and strength

Dosage form: Film coated bi-layered tablet

Strength: Dapagliflozin 10 mg, Glimepiride 1 mg & 2 mg, Metformin Hydrochloride 1000 mg

4. Clinical particulars

4.1 Therapeutic indication

It is indicated as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 Diabetes Mellitus (T2DM).

4.2 Posology and method of administration

Posology

Dose: As directed by the Physician.

Glimepiride

Glimepiride tablets should be administered with breakfast or the first main meal of the day. The recommended starting dose of glimepiride tablet is 1 mg or 2 mg once daily. Patients at increased risk for hypoglycemia (e.g., the elderly or patients with renal impairment) should be started on 1 mg once daily.

After reaching a daily dose of 2 mg, further dose increases can be made in increments of 1 mg or 2 mg based upon the patient's glycemic response. Uptitration should not occur more frequently than every 1 to 2 weeks. A conservative titration scheme is recommended for patients at increased risk for hypoglycemia.

The maximum recommended dose is 8 mg once daily. Patients being transferred to glimepiride from longer half-life sulfonylureas (e.g., chlorpropamide) may have overlapping drug effect for 1 to 2 weeks and should be appropriately monitored for hypoglycemia.

When colesevelam is coadministered with glimepiride, maximum plasma concentration and total exposure to glimepiride is reduced. Therefore, glimepiride should be administered at least 4 hours.

Metformin

Adults with normal renal function ($GFR \geq 90$ mL/min)

Monotherapy and combination with other oral antidiabetic agents:

The usual starting dose is 500 mg, 850 mg and 1000 mg metformin hydrochloride 2 or 3 times daily given during or after meals. After 10 to 15 days the dose should be adjusted on the basis of blood glucose measurements. A slow increase of dose may improve gastrointestinal tolerability.

The maximum recommended dose of metformin hydrochloride is 3 g daily, taken as 3 divided doses.

If transfer from another oral antidiabetic agent is intended: discontinue the other agent and initiate metformin at the dose indicated above.

Combination with insulin:

Metformin and insulin may be used in combination therapy to achieve better blood glucose control. Metformin hydrochloride is given at the usual starting dose of 500 mg, 850 and 1000 mg 2 or 3 times daily, while insulin dosage is adjusted on the basis of blood glucose measurements.

Elderly:

Due to the potential for decreased renal function in elderly subjects, the metformin dosage should be adjusted based on renal function. Regular assessment of renal function is necessary.

Renal impairment

GFR should be assessed before treatment with metformin-containing medicinal products begins and at least every year thereafter. In patients with increased risk of further impairment of renal function and in elderly, renal function should be assessed more often, e.g. every 3-6 months.

GFRml/min	Total maximum daily dose (to be divided into 2-3 doses daily)	To consider
60-89	3000 mg	Dose reduction may be considered in relation to declining renal function.
45-59	2000 mg	Factors that may increase the risk of lactate acidosis should be reviewed before considering initiation of metformin. The starting dose is at most half of the maximum dose
30-44	1000 mg	
< 30		Metformin is contraindicated.

Children and adolescents:

Paediatric population

Monotherapy and combination with insulin

- Metformin can be used in children from 10 years of age and adolescents.
- The usual starting dose is 500 mg, 850 mg and 1000 mg metformin hydrochloride once daily, given during or after meals. After 10 to 15 days the dose should be adjusted on the basis of blood glucose measurements. A slow increase of dose may improve gastrointestinal tolerability. The maximum recommended dose of metformin hydrochloride is 2 g daily, taken as 2 or 3 divided doses.

Dapagliflozin

When dapagliflozin is used in combination with insulin or an insulin secretagogue, such as a sulphonylurea, a lower dose of insulin or insulin secretagogue may be considered to reduce the risk of hypoglycaemia.

Heart failure

In the DAPA-HF study, dapagliflozin was administered in conjunction with other heart failure therapies.

Chronic kidney disease

In the DAPA-CKD study, dapagliflozin was administered in conjunction with other chronic kidney disease related therapies.

Renal impairment

No dose adjustment is required based on renal function.

It is not recommended to initiate treatment with dapagliflozin in patients with an estimated glomerular filtration rate (eGFR) < 15 mL/min/1.73m².

In patients with type 2 diabetes mellitus, the glucose lowering efficacy of dapagliflozin is reduced when eGFR is < 45 mL/min/1.73m², and is likely absent in patients with severe renal impairment. Therefore, if eGFR falls below 45 mL/min/1.73m², additional glucose lowering treatment should be considered in patients with type 2 diabetes mellitus.

Hepatic impairment

No dose adjustment is necessary for patients with mild or moderate hepatic impairment. In patients with severe hepatic impairment, a starting dose of 5 mg is recommended. If well tolerated, the dose may be increased to 10 mg.

Elderly (≥ 65 years)

No dose adjustment is recommended based on age.

Paediatric population

No dose adjustment is required for the treatment of type 2 diabetes mellitus in children aged 10 years and above. No reported data are available for children below 10 years of age.

The safety and efficacy of dapagliflozin for the treatment of heart failure or for the treatment of chronic kidney disease in children < 18 years have not yet been established. No reported data are available.

Method of administration

GLUCRETA GM can be taken with or without food. Tablets are to be swallowed whole.

4.3 Contraindications

Glimepiride

Glimepiride tablet is contraindicated in patients with a history of a hypersensitivity reaction to Glimepiride or any of the product's ingredients

Sulfonamide derivatives: Patients who have developed an allergic reaction to sulfonamide derivatives may develop an allergic reaction to glimepiride. Do not use glimepiride in patients who have a history of an allergic reaction to sulfonamide derivatives.

Metformin

Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis).

- Diabetic pre-coma.
- Sever renal failure (GFR < 30 ml/min).
- Acute conditions with the potential to alter renal function such as: dehydration, severe infection, shock.
- Disease which may cause tissue hypoxia (especially acute disease, or worsening of chronic disease) such as: decompensated heart failure, respiratory failure, recent myocardial infarction, shock.
- Hepatic insufficiency, acute alcohol intoxication, alcoholism.

Dapagliflozin

Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

Glimepiride

Hypoglycemia

All sulfonylureas, including glimepiride, can cause severe hypoglycemia. The patient's ability to concentrate and react may be impaired as a result of hypoglycemia. These impairments may present a risk in situations where these abilities are especially important, such as driving or operating other

machinery. Severe hypoglycemia can lead to unconsciousness or convulsions and may result in temporary or permanent impairment of brain function or death.

Patients must be educated to recognize and manage hypoglycemia. Use caution when initiating and increasing glimepiride doses in patients who may be predisposed to hypoglycemia (e.g., the elderly, patients with renal impairment, patients on other anti-diabetic medications). Debilitated or malnourished patients, and those with adrenal, pituitary, or hepatic impairment are particularly susceptible to the hypoglycemic action of glucose-lowering medications. Hypoglycemia is also more likely to occur when caloric intake is deficient, after severe or prolonged exercise, or when alcohol is ingested. Early warning symptoms of hypoglycemia may be different or less pronounced in patients with autonomic neuropathy, the elderly, and in patients who are taking beta-adrenergic blocking medications or other sympatholytic agents. These situations may result in severe hypoglycemia before the patient is aware of the hypoglycemia.

Hypersensitivity Reactions

There have been postmarketing reports of hypersensitivity reactions in patients treated with glimepiride, including serious reactions such as anaphylaxis, angioedema, and Stevens- Johnson Syndrome. If a hypersensitivity reaction is suspected, promptly discontinue glimepiride, assess for other potential causes for the reaction, and institute alternative treatment for diabetes.

Hemolytic Anemia

Sulfonylureas can cause hemolytic anemia in patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency. Because glimepiride is a sulfonylurea, use caution in patients with G6PD deficiency and consider the use of a non-sulfonylurea alternative. There are also postmarketing reports of haemolytic anemia in patients receiving glimepiride who did not have known G6PD deficiency.

Increased Risk of Cardiovascular Mortality with Sulfonylureas

The administration of oral hypoglycemic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. This warning is based on the study conducted by the University Group Diabetes Program (UGDP), a long-term, prospective clinical trial designed to evaluate the effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in patients with non-insulin-dependent diabetes. The study involved 823 patients who were randomly assigned to one of four treatment groups.

UGDP reported that patients treated for 5 to 8 years with diet plus a fixed dose of tolbutamide (1.5 grams per day) had a rate of cardiovascular mortality approximately 2 and a half times that of patients treated with diet alone. A significant increase in total mortality was not observed, but the use of tolbutamide was discontinued based on the increase in cardiovascular mortality, thus limiting the opportunity for the study to show an increase in overall mortality.

Despite controversy regarding the interpretation of these results, the findings of the UGDP study provide an adequate basis for this warning. The patient should be informed of the potential risks and advantages of glimepiride and of alternative modes of therapy.

Although only one drug in the sulfonylurea class (tolbutamide) was included in this study, it is prudent from a safety standpoint to consider that this warning may also apply to other oral hypoglycemic drugs in this class, in view of their close similarities in mode of action and chemical structure.

Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk

reduction with glimepiride or any other anti-diabetic drug.

Metformin

Lactic acidosis:

Lactic acidosis is a very rare, but serious (high mortality in the absence of prompt treatment), metabolic complication most often occurs at acute worsening of renal function or cardiorespiratory illness or sepsis. Metformin accumulation occurs at acute worsening of renal function and increases the risk of lactic acidosis.

In case of dehydration (severe diarrhoea or vomiting, fever or reduced fluid intake), metformin should be temporarily discontinued and contact with a health care professional is recommended.

Medicinal products that can acutely impair renal function (such as antihypertensives, diuretics and NSAIDs) should be initiated with caution in metformin-treated patients. Other risk factors for lactic acidosis are excessive alcohol intake; hepatic insufficiency, inadequately controlled diabetes, ketosis, prolonged fasting and any condition associated with hypoxia as well as concomitant use of medicinal products that may cause lactic acidosis.

Patients and/or care-givers should be informed of the risk of lactic acidosis. Lactic acidosis is characterised by acidotic dyspnoea muscle cramps, abdominal pain, asthenia, and hypothermia followed by coma. In case of suspected symptoms, the patient should stop taking metformin and seek immediate medical attention. Diagnostic laboratory findings are decreased blood pH (< 7.35), increased plasma lactate levels (5 mmol/l), and an increased anion gap and lactate/pyruvate ratio.

Renal function:

GFR should be assessed before treatment initiation and regularly. Metformin is contraindicated in patients with GFR <30 ml / min and should be temporarily discontinued in presence of conditions that alter renal function..

Cardiac function

Patients with heart failure are more at risk of hypoxia and renal insufficiency. In patients with chronic stable heart failure, metformin may be used with regular monitoring of cardiac and renal function. For patients with acute and unstable heart failure, metformin is contraindicated.

Administration of iodinated contrast media:

Intravascular administration of iodinated contrast agents may lead to contrast-induced nephropathy resulting in metformin accumulation and increased risk of lactate acidosis. Metformin should be discontinued before or at the time of imaging procedure and should not be reinstated until at least 48 hours after, provided that renal function has been evaluated and demonstrated to be stable.

Surgery:

Metformin must be discontinued at the time of surgery under general, spinal or epidural anaesthesia. Therapy may be restarted no earlier than 48 hours following surgery or resumption of oral nutrition and provided that renal function has been reevaluated and found to be stable.

Paediatric population:

The diagnosis of type 2 diabetes mellitus should be confirmed before treatment with metformin is initiated. No effect of metformin on growth and puberty has been detected during controlled clinical studies of one-year duration but no long-term data on these specific points are available. Therefore, a careful follow-up of the effect of metformin on these parameters in metformin-treated children, especially prepubescent children, is recommended.

Children aged between 10 and 12 years:

Only 15 subjects aged between 10 and 12 years were included in the controlled clinical studies conducted in children and adolescents. Although efficacy and safety of metformin in these children did not differ from efficacy and safety in older children and adolescents, particular caution is recommended when prescribing to children aged between 10 and 12 years.

Other precautions:

All patients should continue their diet with a regular distribution of carbohydrate intake during the day. Overweight patients should continue their energy-restricted diet.

The usual laboratory tests for diabetes monitoring should be performed regularly.

Metformin alone does not cause hypoglycaemia, but caution is advised when it is used in combination with insulin or other oral antidiabetics (e.g. sulfonylureas or meglitinides).

Dapagliflozin

Renal impairment

There is limited experience with initiating treatment with dapagliflozin in patients with eGFR < 25 mL/min/1.73m², and no experience with initiating treatment in patients with eGFR < 15 mL/min/1.73m². Therefore, it is not recommended to initiate treatment with dapagliflozin in patients with eGFR < 15 mL/min/1.73m².

The glucose lowering efficacy of dapagliflozin is dependent on renal function, and is reduced in patients with eGFR < 45 mL/min/1.73m² and is likely absent in patients with severe renal impairment.

In patients with moderate renal impairment (eGFR < 60 mL/min/1.73m²), a higher proportion of patients treated with dapagliflozin had adverse reactions of increase in parathyroid hormone (PTH) and hypotension, compared with placebo.

Hepatic impairment

There is limited experience in clinical studies in patients with hepatic impairment. Dapagliflozin exposure is increased in patients with severe hepatic impairment.

Use in patients at risk for volume depletion and/or hypotension

Due to its mechanism of action, dapagliflozin increases diuresis which may lead to the modest decrease in blood pressure observed in clinical studies. It may be more pronounced in patients with very high blood glucose concentrations.

Caution should be exercised in patients for whom a dapagliflozin-induced drop in blood pressure could pose a risk, such as patients on anti-hypertensive therapy with a history of hypotension or elderly patients.

In case of intercurrent conditions that may lead to volume depletion (e.g. gastrointestinal illness), careful monitoring of volume status (e.g. physical examination, blood pressure measurements, laboratory tests including haematocrit and electrolytes) is recommended. Temporary interruption of treatment with dapagliflozin is recommended for patients who develop volume depletion until the depletion is corrected.

Diabetic ketoacidosis

Rare cases of diabetic ketoacidosis (DKA), including life-threatening and fatal cases, have been reported in patients treated with sodium-glucose co-transporter 2 (SGLT2) inhibitors, including dapagliflozin. In a number of cases, the presentation of the condition was atypical with only moderately increased blood glucose values, below 14 mmol/L (250 mg/dL).

The risk of diabetic ketoacidosis must be considered in the event of non-specific symptoms such as nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue or sleepiness. Patients should be assessed for ketoacidosis immediately if these symptoms occur, regardless of blood glucose level.

In patients where DKA is suspected or diagnosed, dapagliflozin treatment should be stopped immediately.

Treatment should be interrupted in patients who are hospitalised for major surgical procedures or acute serious medical illnesses. Monitoring of ketones is recommended in these patients. Measurement of blood ketone levels is preferred to urine. Treatment with dapagliflozin may be restarted when the ketone values are normal and the patient's condition has stabilised.

Before initiating dapagliflozin, factors in the patient history that may predispose to ketoacidosis should be considered.

Patients who may be at higher risk of DKA include patients with a low beta cell function reserve (e.g. type 2 diabetes patients with low C peptide or latent autoimmune diabetes in adults (LADA) or patients with a history of pancreatitis), patients with conditions that lead to restricted food intake or severe dehydration, patients for whom insulin doses are reduced and patients with increased insulin requirements due to acute medical illness, surgery or alcohol abuse. SGLT2 inhibitors should be used with caution in these patients.

Restarting SGLT2 inhibitor treatment in patients experiencing a DKA while on SGLT2 inhibitor treatment is not recommended, unless another clear precipitating factor is identified and resolved.

In type 1 diabetes mellitus studies with dapagliflozin, DKA was reported with common frequency. Dapagliflozin should not be used for treatment of patients with type 1 diabetes.

Necrotising fasciitis of the perineum (Fournier's gangrene)

Postmarketing cases of necrotising fasciitis of the perineum (also known as Fournier's gangrene) have been reported in female and male patients taking SGLT2 inhibitors. This is a rare but serious and potentially life-threatening event that requires urgent surgical intervention and antibiotic treatment.

Patients should be advised to seek medical attention if they experience a combination of symptoms of pain, tenderness, erythema, or swelling in the genital or perineal area, with fever or malaise. Be aware that either uro-genital infection or perineal abscess may precede necrotising fasciitis. If Fournier's gangrene is suspected, Dapagliflozin should be discontinued and prompt treatment (including antibiotics and surgical debridement) should be instituted.

Urinary tract infections

Urinary glucose excretion may be associated with an increased risk of urinary tract infection; therefore, temporary interruption of dapagliflozin should be considered when treating pyelonephritis or *urosepsis*.

Elderly (≥ 65 years)

Elderly patients may be at a greater risk for volume depletion and are more likely to be treated with diuretics.

Elderly patients are more likely to have impaired renal function, and/or to be treated with anti-hypertensive medicinal products that may cause changes in renal function such as angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin II type 1 receptor blockers (ARB). The same recommendations for renal function apply to elderly patients as to all patients.

Cardiac failure

Experience with dapagliflozin in NYHA class IV is limited.

Chronic kidney disease

There is no experience with dapagliflozin for the treatment of chronic kidney disease in patients without diabetes who do not have albuminuria.

Dapagliflozin has not been studied for the treatment of chronic kidney disease in patients with polycystic kidney disease, glomerulonephritis with flares (lupus nephritis or ANCA-associated vasculitis), ongoing or recent requirements of cytotoxic, immunosuppressive or other immunomodulating renal therapy, or in patients who received an organ transplant.

Lower limb amputations

An increase in cases of lower limb amputation (primarily of the toe) has been observed in long-term, clinical studies in type 2 diabetes mellitus with SGLT2 inhibitors. It is unknown whether this constitutes a class effect. It is important to counsel patients with diabetes on routine preventative foot care.

Urine laboratory assessments

Due to its mechanism of action, patients taking Dapagliflozin will test positive for glucose in their urine.

4.5 Drugs interactions

Glimepiride

Drugs Affecting Glucose Metabolism

A number of medications affect glucose metabolism and may require glimepiride dose adjustment and particularly close monitoring for hypoglycemia or worsening glycemic control. The following are examples of medications that may increase the glucose-lowering effect of sulfonylureas including glimepiride, increasing the susceptibility to and/or intensity of hypoglycemia: oral anti-diabetic medications, pramlintide acetate, insulin, angiotensin converting enzyme (ACE) inhibitors, H2 receptor antagonists, fibrates, propoxyphene, pentoxifylline, somatostatin analogs, anabolic steroids and androgens, cyclophosphamide, phenylamidol, guanethidine, fluconazole, sulfapyrazone, tetracyclines, clarithromycin, disopyramide, quinolones, and those drugs that are highly protein-bound, such as fluoxetine, nonsteroidal anti-inflammatory drugs, salicylates, sulfonamides, chloramphenicol, coumarins, probenecid and monoamine oxidase inhibitors.

When these medications are administered to a patient receiving glimepiride, monitor the patient closely for hypoglycemia. When these medications are withdrawn from a patient receiving glimepiride, monitor the patient closely for worsening glycemic control.

The following are examples of medications that may reduce the glucose-lowering effect of sulfonylureas including glimepiride, leading to worsening glycemic control: danazol, glucagon, somatropin, protease inhibitors, atypical antipsychotic medications (e.g., olanzapine and clozapine), barbiturates, diazoxide, laxatives, rifampin, thiazides and other diuretics, corticosteroids, phenothiazines, thyroid hormones, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics (e.g., epinephrine, albuterol, terbutaline), and isoniazid.

When these medications are administered to a patient receiving glimepiride, monitor the patient closely for worsening glycemic control. When these medications are withdrawn from a patient receiving glimepiride, monitor the patient closely for hypoglycemia. Beta-blockers, clonidine, and reserpine may lead to either potentiation or weakening of glimepiride's glucose-

lowering effect. Both acute and chronic alcohol intake may potentiate or weaken the glucose-lowering action of glimepiride in an unpredictable fashion.

The signs of hypoglycemia may be reduced or absent in patients taking sympatholytic drugs such as beta-blockers, clonidine, guanethidine, and reserpine.

Miconazole

A potential interaction between oral miconazole and sulfonylureas leading to severe hypoglycemia has been reported. Whether this interaction also occurs with other dosage forms of miconazole is not known.

Cytochrome P450 2C9 Interactions

There may be an interaction between glimepiride and inhibitors (e.g., fluconazole) and inducers (e.g., rifampin) of cytochrome P450 2C9. Fluconazole may inhibit the metabolism of glimepiride, causing increased plasma concentrations of glimepiride which may lead to hypoglycemia. Rifampin may induce the metabolism of glimepiride, causing decreased plasma concentrations of glimepiride which may lead to worsening glycemic control.

Concomitant Administration of Colesevelam

Colesevelam can reduce the maximum plasma concentration and total exposure of glimepiride when the two are coadministered. However, absorption is not reduced when glimepiride is administered 4 hours prior to colesevelam. Therefore, glimepiride should be administered at least 4 hours prior to colesevelam.

Metformin

Concomitant use not recommended:

Alcohol:

Alcohol intoxication is associated with an increased risk of lactic acidosis, particularly in case of fasting malnutrition or hepatic impairment.

Iodinated contrast agents

Metformin must be discontinued prior to, or at the time of the test and not be restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable.

Combinations requiring precautions for use:

Some medicinal products can adversely affect renal function which may increase the risk of lactic acidosis, e.g. NSAIDs, including selective cyclo-oxygenase (COX) II inhibitors, ACE inhibitors, angiotensin II receptor antagonists and diuretics, especially loop diuretics. When starting or using such products in combination with metformin, close monitoring of renal function is necessary.

Medicinal products with intrinsic hyperglycaemic activity (e.g. glucocorticoids (systemic and local routes) and sympathomimetics):

More frequent blood glucose monitoring may be required, especially at the beginning of treatment. If necessary, adjust the metformin dosage during therapy with the respective medicinal product and upon its discontinuation.

Organic cation transporters (OCT)

Metformin is a substrate of both transporters OCT1 and OCT2.

Co-administration of metformin with

- Inhibitors of OCT1 (such as verapamil) may reduce efficacy of metformin.
- Inducers of OCT1 (such as rifampicin) may increase gastrointestinal absorption and efficacy of metformin.
- Inhibitors of OCT2 (such as cimetidine, dolutegravir, ranolazine, trimethoprim, vandetanib, isavuconazole) may decrease the renal elimination of metformin and thus lead to an increase in metformin plasma concentration.
- Inhibitors of both OCT1 and OCT2 (such as crizotinib, olaparib) may alter efficacy and renal elimination of metformin.

Caution is therefore advised, especially in patients with renal impairment, when these drugs are co-administered with metformin, as metformin plasma concentration may increase. If needed, dose adjustment of metformin may be considered as OCT inhibitors/inducers may alter the efficacy of metformin

Dapagliflozin

Pharmacodynamic interactions

Diuretics

Dapagliflozin may add to the diuretic effect of thiazide and loop diuretics and may increase the risk of dehydration and hypotension.

Insulin and insulin secretagogues

Insulin and insulin secretagogues, such as sulphonylureas, cause hypoglycaemia. Therefore, a lower dose of insulin or an insulin secretagogue may be required to reduce the risk of hypoglycaemia when used in combination with dapagliflozin in patients with type 2 diabetes mellitus.

Pharmacokinetic interactions

The metabolism of dapagliflozin is primarily via glucuronide conjugation mediated by UDP glucuronosyltransferase 1A9 (UGT1A9).

In reported in vitro studies, dapagliflozin neither inhibited cytochrome P450 (CYP) 1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, nor induced CYP1A2, CYP2B6 or CYP3A4. Therefore, dapagliflozin is not expected to alter the metabolic clearance of coadministered medicinal products that are metabolised by these enzymes.

Effect of other medicinal products on dapagliflozin

In reported interaction studies conducted in healthy subjects, using mainly a single-dose design, suggest that the pharmacokinetics of dapagliflozin are not altered by metformin, pioglitazone, sitagliptin, glimepiride, voglibose, hydrochlorothiazide, bumetanide, valsartan, or simvastatin.

Following coadministration of dapagliflozin with rifampicin (an inducer of various active transporters and drug-metabolising enzymes) a 22% decrease in dapagliflozin systemic exposure (AUC) was observed, but with no clinically meaningful effect on 24-hour urinary glucose excretion. No dose adjustment is recommended. A clinically relevant effect with other inducers (e.g. carbamazepine, phenytoin, phenobarbital) is not expected.

Following coadministration of dapagliflozin with mefenamic acid (an inhibitor of UGT1A9), a 55% increase in dapagliflozin systemic exposure was seen, but with no clinically meaningful

effect on 24-hour urinary glucose excretion. No dose adjustment is recommended.

Effect of dapagliflozin on other medicinal products

In reported interaction studies conducted in healthy subjects, using mainly a single-dose design, dapagliflozin did not alter the pharmacokinetics of metformin, pioglitazone, sitagliptin, glimepiride, hydrochlorothiazide, bumetanide, valsartan, digoxin (a P-gp substrate) or warfarin (S-warfarin, a CYP2C9 substrate), or the anticoagulatory effects of warfarin as measured by INR. Combination of a single dose of dapagliflozin 20 mg and simvastatin (a CYP3A4 substrate) resulted in a 19% increase in AUC of simvastatin and 31% increase in AUC of simvastatin acid. The increase in simvastatin and simvastatin acid exposures are not considered clinically relevant.

Interference with 1,5-anhydroglucitol (1,5-AG) assay

Monitoring glycaemic control with 1,5-AG assay is not recommended as measurements of 1,5-AG are unreliable in assessing glycaemic control in patients taking SGLT2 inhibitors. Use of alternative methods to monitor glycaemic control is advised.

Paediatric population

The reported interaction studies have only been performed in adults.

4.6 Use in special populations (such as pregnant women, lactating women, pediatric patients geriatric patients etc.)

Pregnancy

Glimepiride

Available data from a small number of published studies and postmarketing experience with glimepiride use in pregnancy over decades have not identified any drug associated risks for major birth defects, miscarriage, or adverse maternal outcomes. However, sulfonylureas (including glimepiride) cross the placenta and have been associated with neonatal adverse reactions such as hypoglycemia. Therefore, glimepiride should be discontinued at least two weeks before expected delivery. Poorly controlled diabetes in pregnancy is also associated with risks to the mother and Fetus.

Metformin

A limited amount of data from the use of metformin in pregnant women does not indicate an increased risk of congenital abnormalities. Animal studies do not indicate harmful effects with respect to pregnancy, embryonic or fetal development, parturition or postnatal development.

When the patient plans to become pregnant and during pregnancy, it is recommended that diabetes is not treated with metformin but insulin be used to maintain blood glucose levels as close to normal as possible, to reduce the risk of malformations of the fetus.

Dapagliflozin

There are reported no data from the use of dapagliflozin in pregnant women. Studies in rats have shown toxicity to the developing kidney in the time period corresponding to the second and third trimesters of human pregnancy. Therefore, the use of dapagliflozin is not recommended during the second and third trimesters of pregnancy.

When pregnancy is detected, treatment with dapagliflozin should be discontinued.

Breast-feeding

Glimepiride

Breastfed infants of lactating women using glimepiride should be monitored for symptoms of hypoglycemia (see Clinical Considerations). It is not known whether glimepiride is excreted in human milk and there are no data on the effects of glimepiride on milk production. Glimepiride is present in rat milk [see Data]. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for glimepiride and any potential adverse effects on the breastfed child from glimepiride or from the underlying maternal condition.

Metformin

Metformin is excreted into human breast milk. No adverse effects were observed in breastfed newborns/infants. However, as only limited data are available, breastfeeding is not recommended during metformin treatment. A decision on whether to discontinue breast-feeding should be made, taking into account the benefit of breastfeeding and the potential risk to adverse effects on the child.

Dapagliflozin

It is unknown whether dapagliflozin and/or its metabolites are excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of dapagliflozin/metabolites in milk, as well as pharmacologically-mediated effects in nursing offspring. A risk to the newborns/infants cannot be excluded. Dapagliflozin should not be used while breast-feeding.

Fertility

Glimepiride

No data available

Metformin

Fertility of male or female rats was unaffected by metformin when administered at doses as high as 600 mg/kg/day, which is approximately three times the maximum recommended human daily dose based on body surface area comparisons.

Dapagliflozin

The effect of dapagliflozin on fertility in humans has not been studied. In male and female rats, dapagliflozin showed no effects on fertility at any dose tested.

4.7 Effects on ability to drive and use machines

Glimepiride can cause severe hypoglycemia the patient's ability to concentrate and react may be impaired as a result of hypoglycemia. These impairments may present a risk in situations where these abilities are especially important, such as driving or operating other machinery.

Metformin monotherapy does not cause hypoglycaemia and therefore has no effect on the ability to drive or to use machines.

However, patients should be alerted to the risk of hypoglycaemia when metformin is used in combination with other antidiabetic agents (e.g. sulfonylureas, insulin or meglitinides).

Dapagliflozin has no or negligible influence on the ability to drive and use machines. Patients should be alerted to the risk of hypoglycaemia when dapagliflozin is used in combination with a sulphonylurea or insulin.

4.8 Undesirable effects

Glimepiride

Hypoglycemia

Hemolytic anemia

Clinical Trials Experience

Approximately 2,800 patients with type 2 diabetes have been treated with Glimepiride in the controlled clinical trials. In these trials, approximately 1,700 patients were treated with Glimepiride for at least 1 year.

Table 1 summarizes adverse events, other than hypoglycemia, that were reported in 11 pooled placebo-controlled trials, whether or not considered to be possibly or probably related to study medication. Treatment duration ranged from 13 weeks to 12 months. Terms that are reported represent those that occurred at an incidence of $\geq 5\%$ among Glimepiride -treated patients and more commonly than in patients who received placebo.

Table 1: Eleven Pooled Placebo-Controlled Trials ranging from 13 weeks to 12 months : Adverse Events (excluding hypoglycemia) Occurring in $\geq 5\%$ of glimepiride-treated Patients and at a Greater Incidence than with Placebo*

Glimepiride N=745 %		Placebo N=294 %
Headache	8.2	7.8
Accidental Injury	5.8	3.4
Flu Syndrome	5.4	4.4
Nausea	5.0	3.4
Dizziness	5.0	2.4

* Glimepiride doses ranged from 1 to 16 mg administered daily †Insufficient information to determine whether any of the accidental injury events were associated with hypoglycemia.

In a randomized, double-blind, placebo-controlled monotherapy trial of 14 weeks duration, patients already on sulfonylurea therapy underwent a 3-week washout period then were randomized to glimepiride 1 mg, 4 mg, 8 mg or placebo. Patients randomized to glimepiride 4 mg or 8 mg underwent forced-titration from an initial dose of 1 mg to these final doses, as tolerated. The overall incidence of possible hypoglycemia (defined by the presence of at least one symptom that the investigator believed might be related to hypoglycemia; a concurrent glucose measurement was not required) was 4% for glimepiride 1 mg, 17% for glimepiride 4 mg, 16% for glimepiride 8 mg and 0% for placebo. All of these events were self-treated.

In a randomized, double-blind, placebo-controlled monotherapy trial of 22 weeks duration, patients received a starting dose of either 1 mg glimepiride or placebo daily. The dose of glimepiride was titrated to a target fasting plasma glucose of 90 to 150 mg/dL. Final daily doses of glimepiride were 1, 2, 3, 4, 6, or 8 mg. The overall incidence of possible hypoglycemia (as defined above for the 14-week trial) for glimepiride vs. placebo was 19.7% vs. 3.2%. All of these events were self-treated.

Weight gain: glimepiride, like all sulfonylureas, can cause weight gain.

Allergic Reactions: In clinical trials, allergic reactions, such as pruritus, erythema, urticaria, and morbilliform or maculopapular eruptions, occurred in less than 1% of glimepiride- treated patients. These may resolve despite continued treatment with glimepiride. There are postmarketing reports of more serious allergic reactions (e.g., dyspnea, hypotension, shock).

Laboratory Tests

Elevated serum alanine aminotransferase (ALT): In 11 pooled placebo-controlled trials of glimepiride, 1.9% of glimepiride-treated patients and 0.8% of placebo-treated patients developed serum ALT greater than 2 times the upper limit of the reference range.

Postmarketing Experience the following adverse reactions have been identified during post-approval use of Glimepiride. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Serious hypersensitivity reactions, including anaphylaxis, angioedema, and Stevens - Johnson syndrome
- Hemolytic anemia in patients with and without G6PD deficiency
- Impairment of liver function (e.g. with cholestasis and jaundice), as well as hepatitis, which may progress to liver failure.
- Porphyria cutanea tarda, photosensitivity reactions and allergic vasculitis
- Leukopenia, agranulocytosis, aplastic anemia, and pancytopenia
- Thrombocytopenia (including severe cases with platelet count less than 10,000/ μ L) and thrombocytopenic purpura
- Hepatic porphyria reactions and disulfiram-like reactions
- Hyponatremia and syndrome of inappropriate antidiuretic hormone secretion (SIADH), most often in patients who are on other medications or who have medical conditions known to cause hyponatremia or increase release of antidiuretic hormone
- Dysgeusia
- Alopecia

Metformin

During treatment initiation, the most common adverse reactions are nausea, vomiting, diarrhoea, abdominal pain and loss of appetite which resolve spontaneously in most cases. To prevent them, it is recommended to take metformin in 2 or 3 daily doses and to increase slowly the doses.

The following adverse reactions may occur under treatment with metformin. Frequencies are defined as follows

very common: $\geq 1/10$; common $\geq 1/100$, $< 1/10$; uncommon $\geq 1/1,000$, $< 1/100$; rare $\geq 1/10,000$, $< 1/1,000$; very rare $< 1/10,000$.

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Metabolism and nutrition disorders:

Very rare:

Lactic acidosis.

Decrease of vitamin B12 absorption with decrease of serum levels during long-term use of metformin. Consideration of such aetiology is recommended if a patient presents with megaloblastic anaemia.

Nervous system disorders:

Common: Taste disturbance

Gastrointestinal disorders:

Very common: Gastrointestinal disorders such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite. These undesirable effects occur most frequently during initiation of therapy and resolve spontaneously in most cases. To prevent them, it is recommended that metformin be taken in 2 or 3 daily doses during or after meals. A slow increase of the dose may also improve gastrointestinal tolerability.

Hepatobiliary disorders:

Very rare: Isolated reports of liver function tests abnormalities or hepatitis resolving upon metformin discontinuation.

Skin and subcutaneous tissue disorders:

Very rare: Skin reactions such as erythema, pruritus, urticaria

Paediatric population

In published and post marketing data and in controlled clinical studies in a limited paediatric population aged 10-16 years treated during 1 year, adverse event reporting was similar in nature and severity to that reported in adults.

Dapagliflozin

Summary of the safety profile

Type 2 diabetes mellitus

In reported clinical studies in type 2 diabetes, more than 15,000 patients have been treated with dapagliflozin.

The primary assessment of safety and tolerability was conducted in a pre-specified pooled analysis of 13 short-term (up to 24 weeks) placebo-controlled studies with 2,360 subjects treated with dapagliflozin 10 mg and 2,295 treated with placebo.

In reported the dapagliflozin cardiovascular outcomes study in type 2 diabetes mellitus, 8,574 patients received dapagliflozin 10 mg and 8,569 received placebo for a median exposure time of 48 months. In total, there were 30,623 patient-years of exposure to dapagliflozin.

The most frequently reported adverse reactions across the clinical studies were genital infections.

Heart failure

In the dapagliflozin cardiovascular outcome study in patients with heart failure with reduced ejection fraction (DAPA-HF study), 2,368 patients were treated with dapagliflozin 10 mg and 2,368 patients with placebo for a median exposure time of 18 months. The patient population included patients with type 2 diabetes mellitus and without diabetes, and patients with eGFR ≥ 30 mL/min/1.73 m².

The overall safety profile of dapagliflozin in patients with heart failure was consistent with the known safety profile of dapagliflozin.

Chronic kidney disease

In the dapagliflozin renal outcome study in patients with chronic kidney disease (DAPA-CKD), 2,149 patients were treated with dapagliflozin 10 mg and 2,149 patients with placebo for a median exposure time of 27 months. The patient population included patients with type 2 diabetes mellitus and without diabetes, with eGFR ≥ 25 to ≤ 75 mL/min/1.73 m². Treatment was continued if eGFR

fell to levels below 25 mL/min/1.73 m².

The overall safety profile of dapagliflozin in patients with chronic kidney disease was consistent with the known safety profile of dapagliflozin.

Tabulated list of adverse reactions

The following adverse reactions have been identified in the placebo-controlled clinical studies and postmarketing surveillance. None were found to be dose-related. Adverse reactions listed below are classified according to frequency and system organ class (SOC). Frequency categories are defined according to the following convention: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$), and not known (cannot be estimated from the available data).

Table 1. Adverse reactions in placebo-controlled clinical studies and post marketing experience

System organ class	Very common	Common*	Uncommon**	Rare	Very rare
Infections and infestations		Vulvovaginitis, balanitis and related genital infections*, ^{b,c} Urinary tract infection*, ^{b,d}	Fungal infection**		Necrotising fasciitis of the perineum (Fournier's gangrene) ^{b,i}
Metabolism and nutrition disorders	Hypoglycaemia (when used with SU or insulin) ^b		Volume depletion ^{b,e} Thirst**	Diabetic ketoacidosis (when used in type 2 diabetes mellitus) ^{b,i,k}	
Nervous system disorders		Dizziness			
Gastrointestinal disorders			Constipation** Dry mouth**		
Skin and subcutaneous tissue disorders		Rash ^j			Angioedema
Musculoskeletal and connective		Back pain*			

tissue disorders					
Renal and urinary disorders		Dysuria Polyuria*, ^f	Nocturia**		
Reproductive system and breast disorders			Vulvovaginal pruritus** Pruritus genital**		
Investigations		Haematocrit increased ^g Creatinine renal clearance decreased during initial treatment ^b Dyslipidaemia ^h	Blood creatinine increased during initial treatment** ^{, b} Blood urea increased** Weight decreased**		

^aThe table shows up to 24-week (short-term) data regardless of glycaemic rescue.

^bSee corresponding subsection below for additional information.

^cVulvovaginitis, balanitis and related genital infections includes, e.g. the predefined preferred terms: vulvovaginal mycotic infection, vaginal infection, balanitis, genital infection fungal, vulvovaginal candidiasis, vulvovaginitis, balanitis candida, genital candidiasis, genital infection, genital infection male, penile infection, vulvitis, vaginitis bacterial, vulval abscess.

^dUrinary tract infection includes the following preferred terms, listed in order of frequency reported: urinary tract infection, cystitis, Escherichia urinary tract infection, genitourinary tract infection, pyelonephritis, trigonitis, urethritis, kidney infection and prostatitis.

^eVolume depletion includes, e.g. the predefined preferred terms: dehydration, hypovolaemia, hypotension.

^fPolyuria includes the preferred terms: pollakiuria, polyuria, urine output increased.

^gMean changes from baseline in haematocrit were 2.30% for dapagliflozin 10 mg versus -0.33% for placebo. Haematocrit values >55% were reported in 1.3% of the subjects treated with dapagliflozin 10 mg versus 0.4% of placebo subjects.

^hMean percent change from baseline for dapagliflozin 10 mg versus placebo, respectively, was: total cholesterol 2.5% versus 0.0%; HDL cholesterol 6.0% versus 2.7%; LDL cholesterol 2.9% versus -1.0%; triglycerides -2.7% versus -0.7%.

^jAdverse reaction was identified through postmarketing surveillance. Rash includes the following preferred terms, listed in order of frequency in clinical studies: rash, rash generalised, rash pruritic, rash macular, rash maculo-papular, rash pustular, rash vesicular, and rash erythematous. In active- and placebo-controlled clinical studies (dapagliflozin, N=5936, All control, N=3403), the frequency of rash was similar for dapagliflozin (1.4 %) and all control (1.4%), respectively.

^kReported in the cardiovascular outcomes study in patients with type 2 diabetes (DECLARE). Frequency is based on annual rate.

*Reported in $\geq 2\%$ of subjects and $\geq 1\%$ more and at least 3 more subjects treated with dapagliflozin 10 mg compared to placebo.

**Reported by the investigator as possibly related, probably related or related to study treatment and reported in $\geq 0.2\%$ of subjects and $\geq 0.1\%$ more and at least 3 more subjects treated with dapagliflozin 10 mg compared to placebo.

Description of selected adverse reactions

Vulvovaginitis, balanitis and related genital infections

In the reported 13-study safety pool, vulvovaginitis, balanitis and related genital infections were reported in 5.5% and 0.6% of subjects who received dapagliflozin 10 mg and placebo, respectively. Most infections were mild to moderate, and subjects responded to an initial course of standard treatment and rarely resulted in discontinuation from dapagliflozin treatment. These infections were more frequent in females (8.4% and 1.2% for dapagliflozin and placebo, respectively), and subjects with a prior history were more likely to have a recurrent infection.

In the reported DECLARE study, the numbers of patients with serious adverse events of genital infections were few and balanced: 2 patients in each of the dapagliflozin and placebo groups.

In the reported DAPA-HF study, no patient reported serious adverse events of genital infections in the dapagliflozin group and one in the placebo group. There were 7 (0.3%) patients with adverse events leading to discontinuations due to genital infections in the dapagliflozin group and none in the placebo group.

In the reported DAPA-CKD study, there were 3 (0.1%) patients with serious adverse events of genital infections in the dapagliflozin group and none in the placebo group. There were 3 (0.1%) patients with adverse events leading to discontinuation due to genital infections in the dapagliflozin group and none in the placebo group. Serious adverse events of genital infections or adverse events leading to discontinuation due to genital infections were not reported for any patients without diabetes.

Necrotising fasciitis of the perineum (Fournier's gangrene)

Cases of Fournier's gangrene have been reported postmarketing in patients taking SGLT2 inhibitors, including dapagliflozin.

In the DECLARE study with 17,160 type 2 diabetes mellitus patients and a median exposure time of 48 months, a total of 6 cases of Fournier's gangrene were reported, one in the dapagliflozin-treated group and 5 in the placebo group.

Hypoglycaemia

The frequency of hypoglycaemia depended on the type of background therapy used in the clinical studies in diabetes mellitus.

For studies of dapagliflozin in monotherapy, as add-on to metformin or as add-on to sitagliptin (with or without metformin), the frequency of minor episodes of hypoglycaemia was similar ($< 5\%$) between treatment groups, including placebo up to 102 weeks of treatment. Across all studies, major events of hypoglycaemia were uncommon and comparable between the groups treated with dapagliflozin or placebo. Studies with add-on sulphonylurea and add-on insulin therapies had higher rates of hypoglycaemia.

In an add-on to glimepiride study, at weeks 24 and 48, minor episodes of hypoglycaemia were

reported more frequently in the group treated with dapagliflozin 10 mg plus glimepiride (6.0% and 7.9%, respectively) than in the placebo plus glimepiride group (2.1% and 2.1%, respectively).

In an add-on to insulin study, episodes of major hypoglycaemia were reported in 0.5% and 1.0% of subjects treated with dapagliflozin 10 mg plus insulin at weeks 24 and 104, respectively, and in 0.5% of subjects treated with placebo plus insulin groups at weeks 24 and 104. At weeks 24 and 104, minor episodes of hypoglycaemia were reported, respectively, in 40.3% and 53.1% of subjects who received dapagliflozin 10 mg plus insulin and in 34.0% and 41.6% of the subjects who received placebo plus insulin.

In an add-on to metformin and a sulphonylurea study, up to 24 weeks, no episodes of major hypoglycaemia were reported. Minor episodes of hypoglycaemia were reported in 12.8% of subjects who received dapagliflozin 10 mg plus metformin and a sulphonylurea and in 3.7% of subjects who received placebo plus metformin and a sulphonylurea.

In the DECLARE study, no increased risk of major hypoglycaemia was observed with dapagliflozin therapy compared with placebo. Major events of hypoglycaemia were reported in 58 (0.7%) patients treated with dapagliflozin and 83 (1.0%) patients treated with placebo.

In the reported DAPA-HF study, major events of hypoglycaemia were reported in 4 (0.2%) patients in both the dapagliflozin and placebo treatment groups and observed only in patients with type 2 diabetes mellitus.

In the reported DAPA-CKD study, major events of hypoglycaemia were reported in 14 (0.7%) patients in the dapagliflozin group and 28 (1.3%) patients in the placebo group and observed only in patients with type 2 diabetes mellitus.

Volume depletion

In the reported 13-study safety pool, reactions suggestive of volume depletion (including, reports of dehydration, hypovolaemia or hypotension) were reported in 1.1% and 0.7% of subjects who received dapagliflozin 10 mg and placebo, respectively; serious reactions occurred in < 0.2% of subjects balanced between dapagliflozin 10 mg and placebo.

In the reported DECLARE study, the numbers of patients with events suggestive of volume depletion were balanced between treatment groups: 213 (2.5%) and 207 (2.4%) in the dapagliflozin and placebo groups, respectively. Serious adverse events were reported in 81 (0.9%) and 70 (0.8%) in the dapagliflozin and placebo group, respectively. Events were generally balanced between treatment groups across subgroups of age, diuretic use, blood pressure and angiotensin converting enzyme inhibitors (ACE-I)/angiotensin II type 1 receptor blockers (ARB) use. In patients with eGFR < 60 mL/min/1.73 m² at baseline, there were 19 events of serious adverse events suggestive of volume depletion in the dapagliflozin group and 13 events in the placebo group.

In the reported DAPA-HF study, the numbers of patients with events suggestive of volume depletion were 170 (7.2%) in the dapagliflozin group and 153 (6.5%) in the placebo group. There were fewer patients with serious events of symptoms suggestive of volume depletion in the dapagliflozin group (23 [1.0%]) compared with the placebo group (38 [1.6%]). Results were similar irrespective of presence of diabetes at baseline and baseline eGFR.

In the reported DAPA-CKD study, the numbers of patients with events suggestive of volume depletion were 120 (5.6%) in the dapagliflozin group and 84 (3.9%) in the placebo group. There were 16 (0.7%) patients with serious events of symptoms suggestive of volume depletion in the dapagliflozin group and 15 (0.7%) patients in the placebo group.

Diabetic ketoacidosis in type 2 diabetes mellitus

In the reported DECLARE study, with a median exposure time of 48 months, events of DKA were

reported in 27 patients in the dapagliflozin 10 mg group and 12 patients in the placebo group. The events occurred evenly distributed over the study period. Of the 27 patients with DKA events in the dapagliflozin group, 22 had concomitant insulin treatment at the time of the event. Precipitating factors for DKA were as expected in a type 2 diabetes mellitus population.

In the reported DAPA-HF study, events of DKA were reported in 3 patients with type 2 diabetes mellitus in the dapagliflozin group and none in the placebo group.

In the reported DAPA-CKD study, events of DKA were not reported in any patient in the dapagliflozin group and in 2 patients with type 2 diabetes mellitus in the placebo group.

Urinary tract infections

In the reported 13-study safety pool, urinary tract infections were more frequently reported for dapagliflozin 10 mg compared to placebo. Most infections were mild to moderate, and subjects responded to an initial course of standard treatment and rarely resulted in discontinuation from dapagliflozin treatment. These infections were more frequent in females, and subjects with a prior history were more likely to have a recurrent infection.

In the reported DECLARE study, serious events of urinary tract infections were reported less frequently for dapagliflozin 10 mg compared with placebo, 79 (0.9%) events versus 109 (1.3%) events, respectively.

In the reported DAPA-HF study, the numbers of patients with serious adverse events of urinary tract infections were 14 (0.6%) in the dapagliflozin group and 17 (0.7%) in the placebo group. There were 5 (0.2%) patients with adverse events leading to discontinuations due to urinary tract infections in each of the dapagliflozin and placebo groups.

In the reported DAPA-CKD study, the numbers of patients with serious adverse events of urinary tract infections were 29 (1.3%) in the dapagliflozin group and 18 (0.8%) in the placebo group. There were 8 (0.4%) patients with adverse events leading to discontinuations due to urinary tract infections in the dapagliflozin group and 3 (0.1%) in the placebo group. The numbers of patients without diabetes reporting serious adverse events of urinary tract infections or adverse events leading to discontinuation due to urinary tract infections were similar between treatment groups (6 [0.9%] versus 4 [0.6%] for serious adverse events, and 1 [0.1%] versus 0 for adverse events leading to discontinuation, in the dapagliflozin and placebo groups, respectively).

Increased creatinine

Adverse reactions related to increased creatinine were grouped (e.g. decreased renal creatinine clearance, renal impairment, increased blood creatinine and decreased glomerular filtration rate). In the 13-study safety pool, this grouping of reactions was reported in 3.2% and 1.8% of patients who received dapagliflozin 10 mg and placebo, respectively. In patients with normal renal function or mild renal impairment (baseline eGFR \geq 60 mL/min/1.73 m²) this grouping of reactions were reported in 1.3% and 0.8% of patients who received dapagliflozin 10 mg and placebo, respectively. These reactions were more common in patients with baseline eGFR \geq 30 and $<$ 60 mL/min/1.73 m² (18.5% dapagliflozin 10 mg versus 9.3% placebo).

Further evaluation of patients who had renal-related adverse events showed that most had serum creatinine changes of \leq 0.5 mg/dL from baseline. The increases in creatinine were generally transient during continuous treatment or reversible after discontinuation of treatment.

In the reported DECLARE study, including elderly patients and patients with renal impairment (eGFR less than 60 mL/min/1.73 m²), eGFR decreased over time in both treatment groups. At 1 year, mean eGFR was slightly lower, and at 4 years, mean eGFR was slightly higher in the dapagliflozin group compared with the placebo group.

In the reported DAPA-HF study, eGFR decreased over time in both the dapagliflozin group and the placebo group. The initial decrease in mean eGFR was -4.3 mL/min/1.73 m² in the dapagliflozin group and -1.1 mL/min/1.73 m² in the placebo group. At 20 months, change from baseline in eGFR was similar between the treatment groups: -5.3 mL/min/1.73 m² for dapagliflozin and -4.5 mL/min/1.73 m² for placebo.

In the reported DAPA-CKD study, eGFR decreased over time in both the dapagliflozin group and the placebo group. The initial (day 14) decrease in mean eGFR was -4.0 mL/min/1.73 m² in the dapagliflozin group and -0.8 mL/min/1.73 m² in the placebo group. At 28 months, change from baseline in eGFR was -7.4 mL/min/1.73 m² in the dapagliflozin group and -8.6 mL/min/1.73 m² in the placebo group.

Paediatric population

The dapagliflozin safety profile observed in a clinical study in children aged 10 years and above with type 2 diabetes mellitus was similar to that observed in the studies in adults.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are requested to report any suspected adverse reactions via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/index.php/site/info/adverse_event_reporting.

By reporting side effects, you can help provide more information on the safety of this medicine.

4.9 Overdose

Glimepiride

An overdosage of glimepiride, as with other sulfonylureas, can produce severe hypoglycemia. Mild episodes of hypoglycemia can be treated with oral glucose. Severe hypoglycemic reactions constitute medical emergencies requiring immediate treatment. Severe hypoglycemia with coma, seizure, or neurological impairment can be treated with glucagon or intravenous glucose. Continued observation and additional carbohydrate intake may be necessary because hypoglycemia may recur after apparent clinical recovery.

Metformin

Hypoglycaemia has not been seen with metformin hydrochloride doses of up to 85 g, although lactic acidosis has occurred in such circumstances. High overdose of metformin or concomitant risks may lead to lactic acidosis. Lactic acidosis is a medical emergency and must be treated in hospital. The most effective method to remove lactate and metformin is haemodialysis.

Dapagliflozin

Dapagliflozin did not show any toxicity in the reported study where healthy subjects at single oral doses up to 500 mg (50 times the maximum recommended human dose). These subjects had detectable glucose in the urine for a dose-related period of time (at least 5 days for the 500 mg dose), with no reports of dehydration, hypotension or electrolyte imbalance, and with no clinically meaningful effect on QTc interval. The incidence of hypoglycaemia was similar to placebo. In clinical studies where once-daily doses of up to 100 mg (10 times the maximum recommended human dose) were administered for 2 weeks in healthy subjects and type 2 diabetes subjects, the incidence of hypoglycaemia was slightly higher than placebo and was not dose-related. Rates of adverse events including dehydration or hypotension were similar to placebo, and there were no clinically meaningful dose-related changes in laboratory parameters, including serum electrolytes

and biomarkers of renal function.

In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the patient's clinical status. The removal of dapagliflozin by haemodialysis has not been studied.

5. Pharmacological properties

5.1 Mechanism of Action

Glimepiride

Glimepiride primarily lowers blood glucose by stimulating the release of insulin from pancreatic beta cells. Sulfonylureas bind to the sulfonylurea receptor in the pancreatic beta- cell plasma membrane, leading to closure of the ATP-sensitive potassium channel, thereby stimulating the release of insulin.

Metformin

Metformin is a biguanide with antihyperglycaemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia.

Metformin may act via 3 mechanisms:

- 1) reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis.
- 2) in muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilization.
- 3) and delay of intestinal glucose absorption.

Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase.

Metformin increases the transport capacity of all types of membrane glucose transporters (GLUTs) known to date.

Dapagliflozin

Dapagliflozin is a highly potent (K_i : 0.55 nM), selective and reversible inhibitor of SGLT2.

Inhibition of SGLT2 by dapagliflozin reduces reabsorption of glucose from the glomerular filtrate in the proximal renal tubule with a concomitant reduction in sodium reabsorption leading to urinary excretion of glucose and osmotic diuresis. Dapagliflozin therefore increases the delivery of sodium to the distal tubule which increases tubuloglomerular feedback and reduces intraglomerular pressure. This combined with osmotic diuresis leads to a reduction in volume overload, reduced blood pressure, and lower preload and afterload, which may have beneficial effects on cardiac remodelling and preserve renal function. Other effects include an increase in haematocrit and reduction in body weight. The cardiac and renal benefits of dapagliflozin are not solely dependent on the blood glucose-lowering effect and not limited to patients with diabetes as demonstrated in the DAPA-HF and DAPA-CKD studies.

5.2 Pharmacodynamic properties

Glimepiride

In healthy subjects, the time to reach maximal effect (minimum blood glucose concentrations) was approximately 2 to 3 hours after single oral doses of glimepiride. The effects of glimepiride on HbA1c, fasting plasma glucose, and postprandial glucose have been assessed in clinical trials.

Metformin

In clinical studies, use of metformin was associated with either a stable body weight or modest weight loss.

In humans, independently of its action on glycaemia, metformin has favourable effects on lipid metabolism. This has been shown at therapeutic doses in controlled, medium-term or long-term clinical studies: metformin reduces total cholesterol, LDL cholesterol and triglyceride levels.

Dapagliflozin

Increases in the amount of glucose excreted in the urine were observed in healthy subjects and in subjects with type 2 diabetes mellitus following the administration of dapagliflozin. Approximately 70 g of glucose was excreted in the urine per day (corresponding to 280 kcal/day) at a dapagliflozin dose of 10 mg/day in subjects with type 2 diabetes mellitus for 12 weeks. Evidence of sustained glucose excretion was seen in subjects with type 2 diabetes mellitus given dapagliflozin 10 mg/day for up to 2 years.

This urinary glucose excretion with dapagliflozin also results in osmotic diuresis and increases in urinary volume in subjects with type 2 diabetes mellitus. Urinary volume increases in subjects with type 2 diabetes mellitus treated with dapagliflozin 10 mg were sustained at 12 weeks and amounted to approximately 375 mL/day. The increase in urinary volume was associated with a small and transient increase in urinary sodium excretion that was not associated with changes in serum sodium concentrations.

Urinary uric acid excretion was also increased transiently (for 3-7 days) and accompanied by a sustained reduction in serum uric acid concentration. At 24 weeks, reductions in serum uric acid concentrations ranged from -48.3 to -18.3 micromoles/L (-0.87 to -0.33 mg/dL).

5.3 Pharmacokinetic properties

Glimepiride

Absorption

Studies with single oral doses of glimepiride in healthy subjects and with multiple oral doses in patients with type 2 diabetes showed peak drug concentrations (C_{max}) 2 to 3 hours postdose. When glimepiride was given with meals, the mean C_{max} and AUC (area under the curve) were decreased by 8% and 9%, respectively.

Glimepiride does not accumulate in serum following multiple dosing. The pharmacokinetics of glimepiride does not differ between healthy subjects and patients with type 2 diabetes. Clearance of glimepiride after oral administration does not change over the 1 mg to 8 mg dose range, indicating linear pharmacokinetics.

In healthy subjects, the intraindividual and interindividual variabilities of glimepiride pharmacokinetic parameters were 15% to 23% and 24% to 29%, respectively.

Distribution

After intravenous dosing in healthy subjects, the volume of distribution (V_d) was 8.8 L (113 mL/kg), and the total body clearance (CL) was 47.8 mL/min. Protein binding was greater than 99.5%.

Metabolism

Glimepiride is completely metabolized by oxidative biotransformation after either an intravenous or oral dose. The major metabolites are the cyclohexyl hydroxy methyl derivative (M1) and the carboxyl derivative (M2). Cytochrome P450 2C9 is involved in the biotransformation of glimepiride to M1. M1 is further metabolized to M2 by one or several cytosolic enzymes. M2 is inactive. In animals, M1 possesses about one-third of the pharmacological activity of glimepiride, but it is unclear whether M1 results in clinically meaningful effects on blood glucose in humans.

Excretion

When ^{14}C -glimepiride was given orally to 3 healthy male subjects, approximately 60% of the total radioactivity was recovered in the urine in 7 days. M1 and M2 accounted for 80% to 90% of the radioactivity recovered in the urine. The ratio of M1 to M2 in the urine was approximately 3:2 in

two subjects and 4:1 in one subject. Approximately 40% of the total radioactivity was recovered in feces. M1 and M2 accounted for about 70% (ratio of M1 to M2 was 1:3) of the radioactivity recovered in feces. No parent drug was recovered from urine or feces. After intravenous dosing in patients, no significant biliary excretion of glimepiride or its M1 metabolite was observed.

Specific Populations

Geriatric patients

A comparison of glimepiride pharmacokinetics in patients with type 2 diabetes ≤ 65 years and those > 65 years was evaluated in a multiple-dose study using glimepiride 6 mg daily. There were no significant differences in glimepiride pharmacokinetics between the two age groups. The mean AUC at steady state for the older patients was approximately 13% lower than that for the younger patients; the mean weight adjusted clearance for the older patients was approximately 11% higher than that for the younger patients.

Gender

There were no differences between males and females in the pharmacokinetics of glimepiride when adjustment was made for differences in body weight.

Race

No studies have been conducted to assess the effects of race on glimepiride pharmacokinetics but in placebo-controlled trials of glimepiride in patients with type 2 diabetes, the reduction in HbA1C was comparable in Caucasians (n = 536), blacks (n = 63), and Hispanics (n = 63).

Renal impairment

In a single-dose, open-label study glimepiride 3 mg was administered to patients with mild, moderate and severe renal impairment as estimated by creatinine clearance (CL_{Cr}): Group I consisted of 5 patients with mild renal impairment (CL_{Cr} > 50 mL/min), Group II consisted of 3 patients with moderate renal impairment (CL_{Cr} = 20 to 50 mL/min) and Group III consisted of 7 patients with severe renal impairment (CL_{Cr} < 20 mL/min). Although glimepiride serum concentrations decreased max with decreasing renal function, Group III had a 2.3-fold higher mean AUC for M1 and an 8.6-fold higher mean AUC for M2 compared to corresponding mean AUCs in Group I. The apparent terminal half-life (T_{1/2}) for glimepiride did not change, while the half-lives for M1 and M2 increased as renal function decreased. Mean urinary excretion of M1 plus M2 as a percentage of dose decreased from 44.4% for Group I to 21.9% for Group II and 9.3% for Group III.

Hepatic impairment

It is unknown whether there is an effect of hepatic impairment on glimepiride pharmacokinetics because the pharmacokinetics of glimepiride has not been adequately evaluated in patients with hepatic impairment.

Obese patients

The pharmacokinetics of glimepiride and its metabolites were measured in a single-dose study involving 28 patients with type 2 diabetes who either had normal body weight or were morbidly obese. While the t_{1/2}, clearance and volume of distribution of glimepiride in the morbidly obese patients were similar to those in the normal weight group, the morbidly obese had lower C_{max} and AUC than those of normal body weight. The mean C_{max}, AUC₀₋₂₄, AUC_{0-∞} values of glimepiride in normal vs. morbidly obese patients were 547 ± 218 ng/mL vs. 410 ± 124 ng/mL, 3210 ± 1030 hours•ng/mL vs. 2820 ± 1110 hours•ng/mL and 4000 ± 1320 hours•ng/mL vs. 3280 ± 1360 hours•ng/mL, respectively.

Drug Interactions

Aspirin

In a randomized, double-blind, two-period, crossover study, healthy subjects were given either placebo or aspirin 1 gram three times daily for a total treatment period of 5 days. On Day 4 of each

study period, a single 1 mg dose of glimepiride was administered. The glimepiride doses were separated by a 14-day washout period. Coadministration of aspirin and glimepiride resulted in a 34% decrease in the mean glimepiride AUC and a 4% decrease in the mean glimepiride C .

Colesevelam

Concomitant administration of colesevelam and glimepiride resulted in reductions in glimepiride AUC and C of 18% and 8%, respectively. When glimepiride was administered 4 hours prior to colesevelam, there was no significant change in glimepiride AUC or C , -6% and 3%, respectively

Cimetidine and ranitidine

In a randomized, open-label, 3-way crossover study, healthy subjects received either a single 4 mg dose of glimepiride alone, glimepiride with ranitidine (150 mg twice daily for 4 days; glimepiride was administered on Day 3), or glimepiride with cimetidine (800 mg daily for 4 days; glimepiride was administered on Day 3). Co-administration of cimetidine or ranitidine with a single 4 mg oral dose of glimepiride did not significantly alter the absorption and disposition of glimepiride.

Propranolol

In a randomized, double-blind, two-period, crossover study, healthy subjects were given either placebo or propranolol 40 mg three times daily for a total treatment period of 5 days. On Day 4 of each study period, a single 2 mg dose of glimepiride was administered.

The glimepiride doses were separated by a 14-day washout period. Concomitant administration of propranolol and glimepiride significantly increased glimepiride C , AUC, and T by 23%, 22%, and 15%, respectively, and decreased glimepiride CL/f by 18%. The recovery of M1 and M2 from urine was not changed.

Warfarin

In an open-label, two-way, crossover study, healthy subjects received 4 mg of glimepiride daily for 10 days. Single 25 mg doses of warfarin were administered 6 days before starting glimepiride and on Day 4 of glimepiride administration. The concomitant administration of glimepiride did not alter the pharmacokinetics of R- and S-warfarin enantiomers. No changes were observed in warfarin plasma protein binding. Glimepiride resulted in a statistically significant decrease in the pharmacodynamics response to warfarin. The reductions in mean area under the prothrombin time (PT) curve and maximum PT values during glimepiride treatment were 3.3% and 9.9%, respectively, and are unlikely to be clinically relevant.

Metformin

Absorption:

After oral administration, metformin absorption is saturable and incomplete. It is assumed that the pharmacokinetics of metformin absorption is non-linear.

At the recommended metformin doses and dosing schedules, steady state plasma concentrations are reached within 24 to 48 hours and are generally less than 1 microgram/ml. In controlled clinical trials, maximum metformin plasma levels (C_{max}) did not exceed 5 microgram/ml, even at maximum doses.

Distribution:

Plasma protein binding is negligible. Metformin partitions into erythrocytes. The blood peak is lower than the plasma peak and appears at approximately the same time. The red blood cells most likely represent a secondary compartment of distribution. The mean volume of distribution (V_d) ranged between 63-276 l.

Metabolism:

Metformin is excreted unchanged in the urine. No metabolites have been identified in humans.

Elimination:

Renal clearance of metformin is > 400 ml/min, indicating that metformin is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the apparent terminal elimination half-life is approximately 6.5 hours.

When renal function is impaired, renal clearance is decreased in proportion to that of creatinine and thus the elimination half-life is prolonged, leading to increased levels of metformin in plasma.

Characteristics in specific group of patients

Renal impairment

The available data in persons with moderate renal insufficiency are sparse and no reliable estimation of systemic metformin exposure in this subgroup could be made compared to persons with normal renal function. Therefore, dose adjustment should be based on clinical efficacy / tolerability.

Paediatric population

Single dose study: After single doses of metformin hydrochloride 500 mg paediatric patients have shown similar pharmacokinetic profile to that observed in healthy adults. Multiple dose study: Data are restricted to one study. After repeated doses of 500 mg twice daily for 7 days in pediatric patients the peak plasma concentration (C_{max}) and systemic exposure (AUC_{0-t}) were reduced by approximately 33% and 40%, respectively compared to diabetic adults who received repeated doses of 500 mg twice daily for 14 days. As the dose is individually titrated based on glycaemic control, this is of limited clinical relevance.

Dapagliflozin

Absorption

Dapagliflozin was rapidly and well absorbed after oral administration. Maximum dapagliflozin plasma concentrations (C_{max}) were usually attained within 2 hours after administration in the fasted state. Geometric mean steady-state dapagliflozin C_{max} and AUC values following once daily 10 mg doses of dapagliflozin were 158 ng/mL and 628 ng h/mL, respectively. The absolute oral bioavailability of dapagliflozin following the administration of a 10 mg dose is 78%. Administration with a high-fat meal decreased dapagliflozin C_{max} by up to 50% and prolonged T_{max} by approximately 1 hour, but did not alter AUC as compared with the fasted state. These changes are not considered to be clinically meaningful. Hence, Dapagliflozin can be administered with or without food.

Distribution

Dapagliflozin is approximately 91% protein bound. Protein binding was not altered in various disease states (e.g. renal or hepatic impairment). The mean steady-state volume of distribution of dapagliflozin was 118 liters.

Biotransformation

Dapagliflozin is extensively metabolised, primarily to yield dapagliflozin 3-O-glucuronide, which is an inactive metabolite. Dapagliflozin 3-O-glucuronide or other metabolites do not contribute to the glucose-lowering effects. The formation of dapagliflozin 3-O-glucuronide is mediated by UGT1A9, an enzyme present in the liver and kidney, and CYP-mediated metabolism was a minor clearance pathway in humans

Elimination

The mean plasma terminal half-life ($t_{1/2}$) for dapagliflozin was 12.9 hours following a single oral

dose of dapagliflozin 10 mg to healthy subjects. The mean total systemic clearance of dapagliflozin administered intravenously was 207 mL/min. Dapagliflozin and related metabolites are primarily eliminated via urinary excretion with less than 2% as unchanged dapagliflozin. After administration of a 50 mg [14C]-dapagliflozin dose, 96% was recovered, 75% in urine and 21% in faeces. In faeces, approximately 15% of the dose was excreted as parent drug.

Linearity

Dapagliflozin exposure increased proportional to the increment in dapagliflozin dose over the range of 0.1 to 500 mg and its pharmacokinetics did not change with time upon repeated daily dosing for up to 24 weeks.

Characteristics in patients

The pharmacokinetics of Dapagliflozin was generally similar in healthy subjects and in patients with type 2 diabetes.

Renal impairment

At steady-state (20 mg once-daily dapagliflozin for 7 days), subjects with type 2 diabetes mellitus and mild, moderate or severe renal impairment (as determined by iohexol plasma clearance) had mean systemic exposures of dapagliflozin of 32%, 60% and 87% higher, respectively, than those of subjects with type 2 diabetes mellitus and normal renal function. The steady-state 24-hour urinary glucose excretion was highly dependent on renal function and 85, 52, 18 and 11 g of glucose/day was excreted by subjects with type 2 diabetes mellitus and normal renal function or mild, moderate or severe renal impairment, respectively. The impact of haemodialysis on dapagliflozin exposure is not known. The effect of reduced renal function on systemic exposure was evaluated in a population pharmacokinetic model. Consistent with previous results, model predicted AUC was higher in patients with chronic kidney disease compared with patients with normal renal function, and was not meaningfully different in chronic kidney disease patients with type 2 diabetes mellitus and without diabetes.

Hepatic impairment

In reported study subjects with mild or moderate hepatic impairment (Child-Pugh classes A and B), mean C_{max} and AUC of dapagliflozin were up to 12% and 36% higher, respectively, compared to healthy matched control subjects. These differences were not considered to be clinically meaningful. In subjects with severe hepatic impairment (Child-Pugh class C) mean C_{max} and AUC of dapagliflozin were 40% and 67% higher than matched healthy controls, respectively.

Paediatric population

Pharmacokinetics and pharmacodynamics (glucosuria) in children with type 2 diabetes mellitus aged 10-17 years were similar to those observed in adults with type 2 diabetes mellitus.

Gender

The mean dapagliflozin AUCs in reported study females was estimated to be about 22% higher than in males.

Race

There were no reported clinically relevant differences in systemic exposures between White, Black or Asian races.

Body weight

Dapagliflozin exposure was found to decrease with increased weight. Consequently, low-weight patients may have somewhat increased exposure and patients with high weight somewhat

decreased exposure. However, the differences in exposure were not considered clinically meaningful.

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

Glimepiride

Carcinogenesis, Mutagenesis , and Impairment of Fertility

Studies in rats at doses of up to 5000 parts per million (ppm) in complete feed (approximately 340 times the maximum recommended human dose, based on surface area) for 30 months showed no evidence of carcinogenesis. In mice, administration of glimepiride for 24 months resulted in an increase in benign pancreatic adenoma formation that was dose-related and was thought to be the result of chronic pancreatic stimulation.

No adenoma formation in mice was observed at a dose of 320 ppm in complete feed, or 46 to 54 mg/kg body weight/day. This is at least 28 times the maximum human recommended dose of 8 mg once daily based on surface area.

Glimepiride was non-mutagenic in a battery of in vitro and in vivo mutagenicity studies (Ames test, somatic cell mutation, chromosomal aberration, unscheduled DNA synthesis, and mouse micronucleus test).

There was no effect of glimepiride on male mouse fertility in animals exposed up to 2500 mg/kg body weight (>1,500 times the maximum recommended human dose based on surface area). Glimepiride had no effect on the fertility of male and female rats administered up to 4000 mg/kg body weight (approximately 4,000 times the maximum recommended human dose based on surface area).

Metformin

Preclinical data reveal no special hazard for humans based on conventional studies on safety, pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and reproductive toxicity.

Dapagliflozin

In reported non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and fertility. Dapagliflozin did not induce tumours in either mice or rats at any of the doses evaluated in two-year carcinogenicity studies.

Reproductive and developmental toxicity

Direct administration of dapagliflozin to weanling juvenile rats and indirect exposure during late pregnancy (time periods corresponding to the second and third trimesters of pregnancy with respect to human renal maturation) and lactation are each associated with increased incidence and/or severity of renal pelvic and tubular dilatations in progeny.

In a reported juvenile toxicity study, when dapagliflozin was dosed directly to young rats from postnatal day 21 until postnatal day 90, renal pelvic and tubular dilatations were reported at all dose levels; pup exposures at the lowest dose tested were ≥ 15 times the maximum recommended human dose. These findings were associated with dose-related increases in kidney weight and macroscopic kidney enlargement observed at all doses. The renal pelvic and tubular dilatations observed in juvenile animals did not fully reverse within the approximate 1-month recovery period.

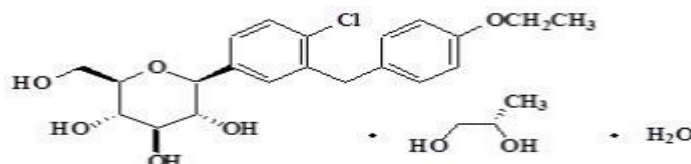
In a reported separate study of pre- and postnatal development, maternal rats were dosed from gestation day 6 through postnatal day 21, and pups were indirectly exposed in utero and throughout lactation. (A satellite study was conducted to assess dapagliflozin exposures in milk and pups.) Increased incidence or severity of renal pelvic dilatation was observed in adult offspring of treated dams, although only at the highest dose tested (associated maternal and pup dapagliflozin exposures were 1,415 times and 137 times, respectively, the human values at the maximum recommended human dose). Additional developmental toxicity was limited to dose-related reductions in pup body weights, and observed only at doses ≥ 15 mg/kg/day (associated with pup exposures that are ≥ 29 times the human values at the maximum recommended human dose). Maternal toxicity was evident only at the highest dose tested, and limited to transient reductions in body weight and food consumption at dose. The no observed adverse effect level (NOAEL) for developmental toxicity, the lowest dose tested, is associated with a maternal systemic exposure multiple that is approximately 19 times the human value at the maximum recommended human dose.

In additional reported studies of embryo-foetal development in rats and rabbits, dapagliflozin was administered for intervals coinciding with the major periods of organogenesis in each species. Neither maternal nor developmental toxicities were observed in rabbits at any dose tested; the highest dose tested is associated with a systemic exposure multiple of approximately 1,191 times the maximum recommended human dose. In rats, dapagliflozin was neither embryolethal nor teratogenic at exposures up to 1,441 times the maximum recommended human dose.

7. Description

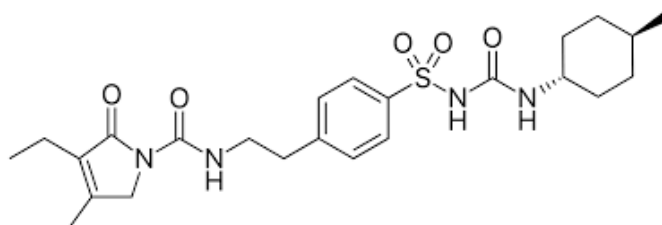
Dapagliflozin Propanediol:

Dapagliflozin Propanediol monohydrate is : D-glucitol, 1,5-anhydro-1-C-[4-chloro-3-[(4-ethoxyphenyl) methyl] phenyl]-, (1S)-, compounded with (2S)-1,2-propanediol, hydrate. The Empirical formula is $C_{21}H_{25}ClO_6 \cdot C_3H_8O_2 \cdot H_2O$ and the molecular weight is 502.98 g/mol. The structural formula is



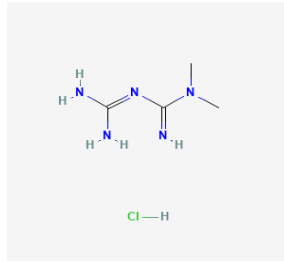
Glimepiride:

Glimepiride is 1-[[4-[2-(3-ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxamido)ethyl]phenyl]sulphonyl]-3-trans-(4-methylcyclohexyl)urea. The empirical formula is $C_{24}H_{34}N_4O_5S$ and the molecular weight is 490.6 g/mol. The structural formula is:



Metformin Hydrochloride:

Metformin Hydrochloride is 1,1-dimethylbiguanide hydrochloride. The empirical formula is $C_4H_{11}N_5, HCl$ and the molecular weight is 165.6 g/mol. The structural formula is:



GLUCRETA GM 1:

Dapagliflozin, glimepiride & Metformin Hydrochloride Extended Release Tablets are White & Orange colored, elongated shaped biconvex film coated bilayered tablets, plain on both sides. The Excipients used are Xanthan gum, Acrypol, Talc, Hydroxy propyl methyl cellulose, Acrypol, Colloidal Silicon dioxide, Magnesium Stearate, Micro Crystalline Cellulose, Lactose monohydrate, polyvinyl pyrrolidone k, Isopropyl alcohol, Dichloromethane, Low Substituted hydroxyl propylcellulose, Crospovidone, Sunset Yellow Lake, Colloidal Silicon dioxide, Directly compressible Lactose, Magnesium Stearate, Dichloromethane.

GLUCRETA GM 2:

Dapagliflozin, glimepiride & Metformin Hydrochloride Extended Release Tablets are White & Yellow colored, elongated shaped biconvex film coated bilayered tablets, plain on both side. The Excipients used are Xanthan gum, Acrypol, Talc, Polyvinyl pyrrolidone k, Hydroxy propyl methylcellulose, Acrypol, Colloidal silicon dioxide, Magneium Stearate, Micro crystalline Cellulose, Lactose Monohydrate, Isopropyl alcohol, dichloromethane, Low substituted hydroxyl propylcellulose, Crospovidone, Quinoline Yellow Lake, Directly compressible lactose.

8. Pharmaceutical particulars

8.1 Incompatibilities

Not applicable

8.2 Shelf-life

Do not use later than date of expiry.

8.3 Packaging information

GLUCRETA GM is available in blister pack of 10 tablets.

8.4 Storage and handing instructions

Store protected from light & moisture at a temperature not exceeding 30⁰C

Keep the medicine out of reach of children

9. Patient Counselling Information

Package leaflet: Information for the user

GLUCRETA GM

Dapagliflozin, Glimepiride, Metformin Hydrochloride (Extended release)Tablets

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.

- | |
|---|
| <ul style="list-style-type: none">• If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. |
|---|

What is in this leaflet

- 9.1 What GLUCRETA GM and what it is used for
- 9.2 What you need to know before you take GLUCRETA GM
- 9.3 How to take GLUCRETA GM
- 9.4 Possible side effects
- 9.5 How to store GLUCRETA GM
- 9.6 Contents of the pack and other information

9.1 What GLUCRETA GM is and what it is used for

GLUCRETA GM contains Glimpiride, Metformin Hydrochloride (ER) & Dapagliflozin Tablets. It is indicated as an adjunct to diet and exercise to improve glycemc control in adult patients with type 2 Diabetes Mellitus (T2DM).

9.2 What you need to know before you take GLUCRETA GM

If you are allergic to Glimpiride, Metformin and Dapagliflozin or any of the other ingredients of this medicine.

Do not take GLUCRETA GM if you're allergic to Glimpiride, Metformin & Dapagliflozin or to any of the other ingredients of this medicine.

If you are not sure, talk to your doctor, pharmacist or nurse before taking **GLUCRETA GM**

Warnings and precautions

Glimpiride

Hypoglycemia

All sulfonylureas, including glimepiride, can cause severe hypoglycemia. The patient's ability to concentrate and react may be impaired as a result of hypoglycemia. These impairments may present a risk in situations where these abilities are especially important, such as driving or operating other machinery. Severe hypoglycemia can lead to unconsciousness or convulsions and may result in temporary or permanent impairment of brain function or death.

Patients must be educated to recognize and manage hypoglycemia. Use caution when initiating and increasing glimepiride doses in patients who may be predisposed to hypoglycemia (e.g., the elderly, patients with renal impairment, patients on other anti-diabetic medications). Debilitated or malnourished patients, and those with adrenal, pituitary, or hepatic impairment are particularly susceptible to the hypoglycemic action of glucose-lowering medications. Hypoglycemia is also more likely to occur when caloric intake is deficient, after severe or prolonged exercise, or when alcohol is ingested. Early warning symptoms of hypoglycemia may be different or less pronounced in patients with autonomic neuropathy, the elderly, and in patients who are taking beta-adrenergic blocking medications or other sympatholytic agents. These situations may result in severe hypoglycemia before the patient is aware of the hypoglycemia.

Hypersensitivity Reactions

There have been postmarketing reports of hypersensitivity reactions in patients treated with glimepiride, including serious reactions such as anaphylaxis, angioedema, and Stevens- Johnson

Syndrome. If a hypersensitivity reaction is suspected, promptly discontinue glimepiride, assess for other potential causes for the reaction, and institute alternative treatment for diabetes.

Hemolytic Anemia

Sulfonylureas can cause hemolytic anemia in patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency. Because glimepiride is a sulfonylurea, use caution in patients with G6PD deficiency and consider the use of a non-sulfonylurea alternative. There are also postmarketing reports of haemolytic anemia in patients receiving glimepiride who did not have known G6PD deficiency.

Increased Risk of Cardiovascular Mortality with Sulfonylureas

The administration of oral hypoglycemic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. This warning is based on the study conducted by the University Group Diabetes Program (UGDP), a long-term, prospective clinical trial designed to evaluate the effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in patients with non-insulin-dependent diabetes. The study involved 823 patients who were randomly assigned to one of four treatment groups.

UGDP reported that patients treated for 5 to 8 years with diet plus a fixed dose of tolbutamide (1.5 grams per day) had a rate of cardiovascular mortality approximately 2 and a half times that of patients treated with diet alone. A significant increase in total mortality was not observed, but the use of tolbutamide was discontinued based on the increase in cardiovascular mortality, thus limiting the opportunity for the study to show an increase in overall mortality.

Despite controversy regarding the interpretation of these results, the findings of the UGDP study provide an adequate basis for this warning. The patient should be informed of the potential risks and advantages of glimepiride and of alternative modes of therapy.

Although only one drug in the sulfonylurea class (tolbutamide) was included in this study, it is prudent from a safety standpoint to consider that this warning may also apply to other oral hypoglycemic drugs in this class, in view of their close similarities in mode of action and chemical structure.

Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with glimepiride or any other anti-diabetic drug.

Metformin

Lactic acidosis:

Lactic acidosis is a very rare, but serious (high mortality in the absence of prompt treatment), metabolic complication most often occurs at acute worsening of renal function or cardiorespiratory illness or sepsis. Metformin accumulation occurs at acute worsening of renal function and increases the risk of lactic acidosis.

In case of dehydration (severe diarrhoea or vomiting, fever or reduced fluid intake), metformin should be temporarily discontinued and contact with a health care professional is recommended.

Medicinal products that can acutely impair renal function (such as antihypertensives, diuretics and NSAIDs) should be initiated with caution in metformin-treated patients. Other risk factors for lactic acidosis are excessive alcohol intake; hepatic insufficiency, inadequately controlled diabetes, ketosis, prolonged fasting and any condition associated with hypoxia as well as concomitant use of medicinal products that may cause lactic acidosis.

Patients and/or care-givers should be informed of the risk of lactic acidosis. Lactic acidosis is characterised by acidotic dyspnoea muscle cramps, abdominal pain, asthenia, and hypothermia followed by coma. In case of suspected symptoms, the patient should stop taking metformin and seek immediate medical attention. Diagnostic laboratory findings are decreased blood pH (< 7.35), increased plasma lactate levels (5 mmol/l), and an increased anion gap and lactate/pyruvate ratio.

Renal function:

GFR should be assessed before treatment initiation and regularly. Metformin is contraindicated in patients with GFR <30 ml / min and should be temporarily discontinued in presence of conditions that alter renal function..

Cardiac function

Patients with heart failure are more at risk of hypoxia and renal insufficiency. In patients with chronic stable heart failure, metformin may be used with regular monitoring of cardiac and renal function. For patients with acute and unstable heart failure, metformin is contraindicated.

Administration of iodinated contrast media:

Intravascular administration of iodinated contrast agents may lead to contrast-induced nephropathy resulting in metformin accumulation and increased risk of lactate acidosis. Metformin should be discontinued before or at the time of imaging procedure and should not be reinstated until at least 48 hours after, provided that renal function has been evaluated and demonstrated to be stable.

Surgery:

Metformin must be discontinued at the time of surgery under general, spinal or epidural anaesthesia. Therapy may be restarted no earlier than 48 hours following surgery or resumption of oral nutrition and provided that renal function has been reevaluated and found to be stable.

Paediatric population:

The diagnosis of type 2 diabetes mellitus should be confirmed before treatment with metformin is initiated. No effect of metformin on growth and puberty has been detected during controlled clinical studies of one-year duration but no long-term data on these specific points are available. Therefore, a careful follow-up of the effect of metformin on these parameters in metformin-treated children, especially prepubescent children, is recommended.

Children aged between 10 and 12 years:

Only 15 subjects aged between 10 and 12 years were included in the controlled clinical studies conducted in children and adolescents. Although efficacy and safety of metformin in these children did not differ from efficacy and safety in older children and adolescents, particular caution is recommended when prescribing to children aged between 10 and 12 years.

Other precautions:

All patients should continue their diet with a regular distribution of carbohydrate intake during the day. Overweight patients should continue their energy-restricted diet.

The usual laboratory tests for diabetes monitoring should be performed regularly.

Metformin alone does not cause hypoglycaemia, but caution is advised when it is used in combination with insulin or other oral antidiabetics (e.g. sulfonylureas or meglitinides).

Dapagliflozin

Renal impairment

There is limited experience with initiating treatment with dapagliflozin in patients with eGFR < 25

mL/min/1.73m², and no experience with initiating treatment in patients with eGFR < 15 mL/min/1.73m². Therefore, it is not recommended to initiate treatment with dapagliflozin in patients with eGFR < 15 mL/min/1.73m².

The glucose lowering efficacy of dapagliflozin is dependent on renal function, and is reduced in patients with eGFR < 45 mL/min/1.73m² and is likely absent in patients with severe renal impairment.

In patients with moderate renal impairment (eGFR < 60 mL/min/1.73m²), a higher proportion of patients treated with dapagliflozin had adverse reactions of increase in parathyroid hormone (PTH) and hypotension, compared with placebo.

Hepatic impairment

There is limited experience in clinical studies in patients with hepatic impairment. Dapagliflozin exposure is increased in patients with severe hepatic impairment.

Use in patients at risk for volume depletion and/or hypotension

Due to its mechanism of action, dapagliflozin increases diuresis which may lead to the modest decrease in blood pressure observed in clinical studies. It may be more pronounced in patients with very high blood glucose concentrations.

Caution should be exercised in patients for whom a dapagliflozin-induced drop in blood pressure could pose a risk, such as patients on anti-hypertensive therapy with a history of hypotension or elderly patients.

In case of intercurrent conditions that may lead to volume depletion (e.g. gastrointestinal illness), careful monitoring of volume status (e.g. physical examination, blood pressure measurements, laboratory tests including haematocrit and electrolytes) is recommended. Temporary interruption of treatment with dapagliflozin is recommended for patients who develop volume depletion until the depletion is corrected.

Diabetic ketoacidosis

Rare cases of diabetic ketoacidosis (DKA), including life-threatening and fatal cases, have been reported in patients treated with sodium-glucose co-transporter 2 (SGLT2) inhibitors, including dapagliflozin. In a number of cases, the presentation of the condition was atypical with only moderately increased blood glucose values, below 14 mmol/L (250 mg/dL).

The risk of diabetic ketoacidosis must be considered in the event of non-specific symptoms such as nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue or sleepiness. Patients should be assessed for ketoacidosis immediately if these symptoms occur, regardless of blood glucose level.

In patients where DKA is suspected or diagnosed, dapagliflozin treatment should be stopped immediately.

Treatment should be interrupted in patients who are hospitalised for major surgical procedures or acute serious medical illnesses. Monitoring of ketones is recommended in these patients. Measurement of blood ketone levels is preferred to urine. Treatment with dapagliflozin may be restarted when the ketone values are normal and the patient's condition has stabilised.

Before initiating dapagliflozin, factors in the patient history that may predispose to ketoacidosis should be considered.

Patients who may be at higher risk of DKA include patients with a low beta cell function reserve (e.g. type 2 diabetes patients with low C peptide or latent autoimmune diabetes in adults (LADA) or patients with a history of pancreatitis), patients with conditions that lead to restricted food intake

or severe dehydration, patients for whom insulin doses are reduced and patients with increased insulin requirements due to acute medical illness, surgery or alcohol abuse. SGLT2 inhibitors should be used with caution in these patients.

Restarting SGLT2 inhibitor treatment in patients experiencing a DKA while on SGLT2 inhibitor treatment is not recommended, unless another clear precipitating factor is identified and resolved.

In type 1 diabetes mellitus studies with dapagliflozin, DKA was reported with common frequency. Dapagliflozin should not be used for treatment of patients with type 1 diabetes.

Necrotising fasciitis of the perineum (Fournier's gangrene)

Postmarketing cases of necrotising fasciitis of the perineum (also known as Fournier's gangrene) have been reported in female and male patients taking SGLT2 inhibitors. This is a rare but serious and potentially life-threatening event that requires urgent surgical intervention and antibiotic treatment.

Patients should be advised to seek medical attention if they experience a combination of symptoms of pain, tenderness, erythema, or swelling in the genital or perineal area, with fever or malaise. Be aware that either uro-genital infection or perineal abscess may precede necrotising fasciitis. If Fournier's gangrene is suspected, Dapagliflozin should be discontinued and prompt treatment (including antibiotics and surgical debridement) should be instituted.

Urinary tract infections

Urinary glucose excretion may be associated with an increased risk of urinary tract infection; therefore, temporary interruption of dapagliflozin should be considered when treating pyelonephritis or *urosepsis*.

Elderly (≥ 65 years)

Elderly patients may be at a greater risk for volume depletion and are more likely to be treated with diuretics.

Elderly patients are more likely to have impaired renal function, and/or to be treated with anti-hypertensive medicinal products that may cause changes in renal function such as angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin II type 1 receptor blockers (ARB). The same recommendations for renal function apply to elderly patients as to all patients.

Cardiac failure

Experience with dapagliflozin in NYHA class IV is limited.

Chronic kidney disease

There is no experience with dapagliflozin for the treatment of chronic kidney disease in patients without diabetes who do not have albuminuria.

Dapagliflozin has not been studied for the treatment of chronic kidney disease in patients with polycystic kidney disease, glomerulonephritis with flares (lupus nephritis or ANCA-associated vasculitis), ongoing or recent requirements of cytotoxic, immunosuppressive or other immunomodulating renal therapy, or in patients who received an organ transplant.

Lower limb amputations

An increase in cases of lower limb amputation (primarily of the toe) has been observed in long-term, clinical studies in type 2 diabetes mellitus with SGLT2 inhibitors. It is unknown whether this constitutes a class effect. It is important to counsel patients with diabetes on routine preventative foot care.

Urine laboratory assessments

Due to its mechanism of action, patients taking Dapagliflozin will test positive for glucose in their urine.

9.3 How to take GLUCRETA GM

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Your doctor will prescribe the strength that is right for you.

If you take more GLUCRETA GM than you should

If you take more than the prescribed dosage of this medicine, contact your doctor immediately.

If you forget to take GLUCRETA GM

If you miss a dose, take it as soon as you remember. If you do not remember until it is time for your next dose, skip the missed dose and go back to your regular schedule. Do not take a double dose of this medicine.

If you stop taking GLUCRETA GM

Continue to take this medicine as long as your doctor prescribes it so you can continue to help control your blood sugar. You should not stop taking this medicine without talking to your doctor first.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

9.4 Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

STOP taking GLUCRETA GM and contact a doctor immediately if you notice any of the following serious side effects:

Glimepiride

Hypoglycemia

Hemolytic anemia

Headache

Accidental Injury

Flu Syndrome

Nausea

Dizziness

Weight gain

Allergic Reactions

Serious hypersensitivity reactions

Hemolytic anemia in patients with and without G6PD deficiency

Impairment of liver function (e.g. with cholestasis and jaundice), as well as hepatitis, which may progress to liver failure.

Porphyria cutanea tarda, photosensitivity reactions and allergic vasculitis

Leukopenia, agranulocytosis, aplastic anemia, and pancytopenia

Thrombocytopenia (including severe cases with platelet count less than 10,000/ μ L) and thrombocytopenic purpura

Hepatic porphyria reactions and disulfiram-like reactions

Hyponatremia and syndrome of inappropriate antidiuretic hormone secretion (SIADH), most often in patients who are on other medications or who have medical conditions known to cause hyponatremia or increase release of antidiuretic hormone

Dysgeusia

Alopecia

Metformin

Nausea, vomiting, diarrhoea, abdominal pain and loss of appetite.

Lactic acidosis.

Decrease of vitamin B12 absorption with decrease of serum levels during long-term use of metformin.

Taste disturbance

Liver function tests abnormalities or hepatitis

Skin reactions such as erythema, pruritus, urticaria.

Dapagliflozin

The most frequently reported adverse reactions are

Vulvovaginitis, balanitis and related genital infections

Urinary tract infection

Heart failure

Increased creatinine

Dehydration,

Hypovolaemia

Hypotension

Hypoglycaemia

Dizziness

Rash

Back pain

Dysuria

Polyuria

Haematocrit increasedg

Decreased Creatinine renal clearance

Dyslipidaemia

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are requested to report any suspected adverse reactions via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/index.php/site/info/adverse_event_reporting.

By reporting side effects, you can help provide more information on the safety of this medicine.

9.5 How to store GLUCRETA GM

Store protected from light & moisture at a temperature not exceeding 30°C.

9.6 Contents of the pack and other information

What GLUCRETA GM contains

GLUCRETA GM contain Dapagliflozin USP, Glimepride IP and Metformin hydrochloride IP As active ingredients of 10 mg, 1/2 mg and 1000 mg Respectively

GLUCRETA GM 1

The Excipients used are Xanthan gum, Acrypol, Talc, Polyvinyl pyrrolidone K, Hydroxy propyl methyl cellulose, Acrypol, Colloidal Silicon dioxide, Magnesium Stearate, Micro Crystalline Cellulose, Lactose monohydrate, Isopropyl alcohol, Dichloromethane, Low Substitud hydroxyl propylcellulose, Crospovidone, Sunset Yellow Lake, Colloidal Silicon dioxide, Directly compressible Lactose, Magnesium Stearate, Dichloromethane.

GLUCRETA GM 2

The Excipients used are Xanthan gum, Acrypol, Talc, Polyvinyl pyrrolidone k, Hydroxy propyl methyl cellulose, Acrypol, Colloidal silicon dioxide, Magneium Stearate, Micro crystalline Cellulose, Lactose Monohydrate, Isopropyl alcohol, dichloromethane, Low substituted hydroxyl propylcellulose, Crospovidone, Quinoline Yellow Lake, Directly compressible lactose.

What GLUCRETA GM looks like and contents of the pack

GLUCRETA GM is available in blister pack of 10 tablets.

10. Details of manufacturer

Mascot Health Series Pvt. Ltd.

Plot No. 79,80, Sector-6A,IIE,Sidcul,Haridwar-249403

11. Details of permission or licence number with date

Mfg. Licence. No.: 68/UA/2009 issued on -11.12.2023

12. Date of revision

NA

MARKETED BY



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IN/GLUCRETA GM /Dec-23/01/PI